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Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979

(*Bacillus anthracis*/hemorrhagic mediastinitis/hemorrhagic thoracic lymphadenitis/epidemic/Russia)

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ABSTRACT **A large epidemic of anthrax that occurred in Sverdlovsk (now Ekaterinburg), Russia, in 1979 resulted in the deaths of many persons. A series of 42 necropsies, representing a majority of the fatalities from this outbreak, consistently revealed pathologic lesions diagnostic of inhalational anthrax, namely hemorrhagic necrosis of the thoracic lymph nodes in the lymphatic drainage of the lungs and hemorrhagic mediastinitis. *Bacillus anthracis* was recovered in bacterial cultures of 20 cases, and organisms were detected microscopically in the infected tissues of nearly all of the cases. A novel observation was primary focal hemorrhagic necrotizing pneumonia at the apparent portal of entry in 11 cases. Mesenteric lymphadenitis occurred in only 9 cases. This remarkably large series demonstrated the full range of effects of anthrax bacteremia and toxemia (edema especially adjacent to sites of extensive infection and pleural effusions) and hematogenously disseminated infection [hemorrhagic meningitis (21 cases) and multiple gastrointestinal submucosal hemorrhagic lesions (39 cases)].**

Beginning early in April 1979, there was a sudden outbreak of an unknown disease among the population of Sverdlovsk in the former Union of Soviet Socialist Republics. In this large industrial city just east of the Ural Mountains, the majority of the patients resided in a limited area on the southern edge of the municipality. International interest was drawn by the suspicion that the epidemic might have resulted from release of a biologic agent from a military facility located in the district where the majority of the patients lived. A publication in May 1980 attributed the epidemic to cutaneous and gastrointestinal exposure to meat from animals infected with *Bacillus anthracis* (1).

Little further information has been published. In fact, the hospital records of the patients affected by this outbreak including the autopsy reports were removed from the hospital. Notes describing the details of the gross observations in the organs at the autopsies of 42 persons in this epidemic were kept in the personal possession of two of the participating pathologists (F.A.A. and L.M.G.). The microscopic slides, paraffin blocks, and tissue samples from the necropsies were also kept in a secure location. A substantial collection of representative examples of the diseased organs was also maintained for demonstration. A series of detailed articles on the macroscopic lesions, microscopic lesions, and causes of death will be published in the Russian medical literature (2). This preliminary report has the purpose of providing in the English language the major observations in a timely manner.

MATERIALS AND METHODS

During the period of 1 week in June 1992, the four authors reexamined together the glass microscopic slides and the available gross organs and evaluated the correlations with notes made in 1979 of the gross descriptions of each necropsy and the microscopic observations for that case. Cultures had been taken for identification of bacterial agents. Bacteria were searched for microscopically in sections stained with hematoxylin and eosin in all cases. Sections cut from six blocks were stained by the Brown–Brenn and Brown–Hopps methods for demonstration of Gram-positive and Gram-negative bacteria (3, 4).

RESULTS

The initial diagnosis of anthrax was made by the pathologist (F.A.A.) in case 1 of this series on the basis of the remarkably hemorrhagic meningitis in a patient who died on approximately the sixth day of the epidemic. The diagnosis was confirmed by demonstration of bacilli on smears prepared at necropsy on the same day (April 10, 1979) and definitively documented by identification of *B. anthracis* in cultures on April 11.

This series of 42 autopsies represents a striking illness affecting previously healthy persons, who died usually after a rapid course of 1–4 days duration (Table 1). All 42 cases were characterized by the most prominent and consistent lesions of hemorrhagic thoracic lymphadenitis (Figs. 1–3) and hemorrhagic mediastinitis (Figs. 3 and 4). Spread of *B. anthracis* to the peribronchial lymph nodes by the lymphatic vessels was emphasized by the presence of the organisms in the marginal sinus where the afferent lymph first enters the lymph node (Fig. 5). The pulmonary portal of entry was further emphasized by the presence of a primary anthrax pulmonary focus—i.e., focal hemorrhagic, necrotizing anthrax pneumonia in 11 patients.

There were various manifestations of hematogenous spread of *B. anthracis* infection including serohemorrhagic and hemorrhagic leptomeningitis (21 cases) (Figs. 6 and 7). Gastrointestinal lesions were observed in 39 cases, most of which appeared to represent multifocal hematogenous spread of *B. anthracis* to the submucosa of the gastrointestinal tract, in particular to the small intestine, stomach, and colon (Figs. 8 and 9). The lesions did not involve the Peyer's patches. Mesenteric lymph nodes demonstrated hemorrhagic involvement in only 9 cases.

A remarkable effect of the disease was edema and other evidence of increased vascular permeability including gelatinous edema of the mediastinum, pleural effusions, leptomeningeal edema, and pulmonary edema. *B. anthracis* was observed in the lesions of serohemorrhagic nature, and anthrax toxins secreted by these organisms were considered to be the cause of the vascular damage resulting in hemorrhage and serious exudate.

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Table 1. Forty-two patients with inhalational anthrax in Sverdlovsk in 1979

No.	Age/ sex	Date			*B. anthracis* identification		Pathology		
		Onset	Admission	Death	Culture	Histology	HEM LN*	HEM MED†	MEN‡
1	42/M	4/7	4/10	4/10	+	+	+	+	+
2	67/M	4/7	4/8	4/9	§	¶	+	+	+
3	68/F	4/8	4/9	4/10	+	+	+	+	+
4	38/M	¶	4/8	4/8	§	§	+	+	§
5	47/M	¶	¶	4/12	+	+	+	+	+
6	68/M	4/9	¶	4/13	−	+	+	+	+
7	25/F	4/10	4/12	4/13	+	+	+	+	+
8	66/F	4/10	4/13	4/13	+	+	+	+	+
9	50/M	4/12	4/13	4/13	−	+	+	+	−
10	65/M	4/10	4/13	4/14	−	+	+	+	−
11	48/M	4/11	4/13	4/14	−	+	+	+	§
12	42/M	¶	4/13	4/14	+	+	+	+	+
13	40/M	¶	¶	4/14	+	+	+	+	+
14	52/M	¶	¶	4/14	+	+	+	+	+
15	37/M	4/12	4/13	4/15	−	+	+	+	−
16	32/M	4/10	4/13	4/15	−	+	+	+	§
17	52/M	4/13	4/14	4/16	−	+	+	+	−
18	68/F	¶	4/16	4/16	−	¶	+	+	−
19	71/F	¶	¶	4/15	−	+	+	+	+
20	58/F	4/15	¶	4/25	−	−	+	+	−
21	42/F	¶	4/13	4/17	−	+	+	+	−
22	49/M	¶	4/16	4/16	+	+	+	+	+
23	43/M	4/14	4/15	4/16	−	+	+	+	§
24	68/F	4/14	4/22	4/30	−	−	+	+	−
25	44/M	4/15	¶	4/18	+	+	+	+	+
26	39/M	4/15	¶	4/19	+	+	+	+	−
27	46/M	4/15	¶	4/21	+	+	+	+	−
28	50/F	4/17	4/21	4/25	−	+	+	+	−
29	45/M	¶	¶	4/22	−	+	+	+	+
30	39/M	4/20	¶	4/23	+	+	+	+	+
31	42/M	4/21	4/23	4/24	−	+	+	+	−
32	42/M	4/21	4/24	4/24	+	+	+	+	−
33	48/M	4/22	¶	4/24	+	+	+	+	+
34	33/M	4/25	¶	5/3	−	¶	+	+	−
35	32/M	¶	4/28	4/28	+	+	+	+	−
36	55/M	4/27	5/1	5/1	−	+	+	+	+
37	33/M	4/29	4/30	4/30	+	+	+	+	+
38	43/M	5/4	5/6	5/10	−	¶	+	+	−
39	25/M	5/7	5/12	5/12	+	+	+	+	+
40	30/M	5/9	¶	5/10	+	+	+	+	+
41	29/M	5/12	5/15	5/16	−	+	+	+	+
42	¶/M	¶	¶	‖	+	+	+	+	−

*Hemorrhagic thoracic lymphadenitis.
†Hemorrhagic mediastinitis.
‡Serohemorrhagic and hemorrhagic meningitis.
§Not examined.
¶Unknown.
‖Found dead and autopsied on 6/15, with preservation of tissues and condition of the body suggesting a short interval between death and necropsy.

DISCUSSION

The pattern of lesions in these 42 cases of fatal anthrax bacteremia and toxemia from Sverdlovsk is typical of inhalational anthrax in experimentally infected nonhuman primates (5) and in epidemiologically diagnosed humans (6–13). The pathogenesis of *B. anthracis* infection that enters via the normal lung begins with transport of spores to the peribronchial and mediastinal lymph nodes (8, 14). After germination of the spores, the bacteria replicate and secrete the three components of the toxin: protective antigen, edema factor, and lethal factor (15–17). Thus, inhalational anthrax is characterized by the severe local effects of the toxin at its primary site of production, thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis, as well as the systemic effects of bacteremia and toxemia. These thoracic lesions are not expected to occur in toxemic cutaneous or intestinal anthrax because spread from the cutaneous or intestinal portal of entry by the lymphatic vessels would involve the regional lymphatic drainage of the primary skin or intestinal lesion, but there would be no spread to the lymphatic drainage of the lungs in the mediastinum. In 11 cases of the present series, there was a single primary pulmonary lesion analogous to the Ghon focus in the more slowly developing infection, tuberculosis.

The gastrointestinal lesions appear to be mainly, or possibly wholly, hematogenous in origin. The lesions are cen-

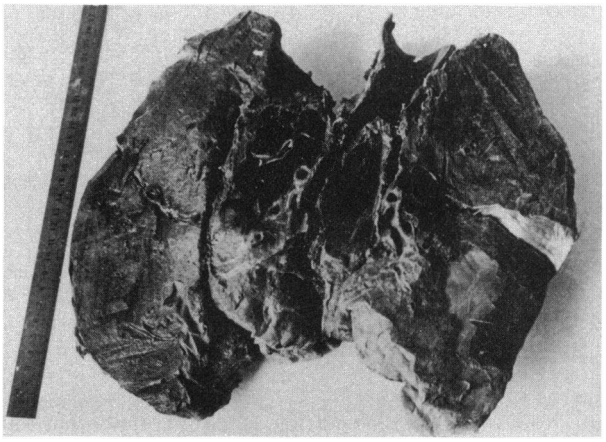

FIG. 1. The cut surface of the lungs, trachea, and hilar lymph nodes in case 41 reveals massive hemorrhagic enlargement of the peribronchial and carinal lymph nodes with extension of the hemorrhage into the adjacent tissues including the submucosa of the bronchi and trachea.

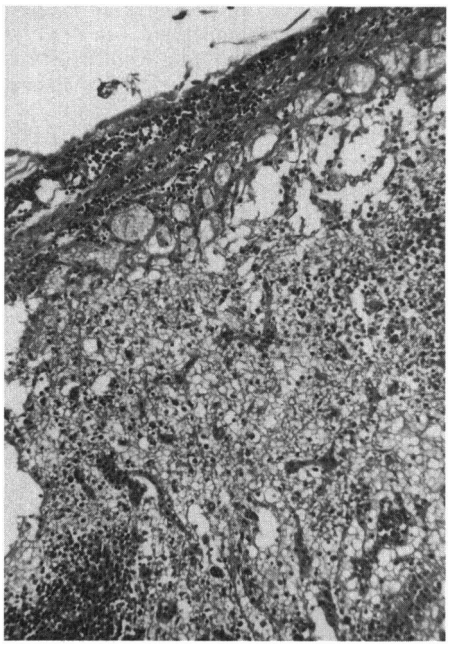

FIG. 2. Photomicrograph of a peribronchial lymph node of case 39 reveals marked dilation of the marginal and draining sinuses because of the presence of protein-rich edema and hemorrhage. (Hematoxylin–eosin stain; ×90.)

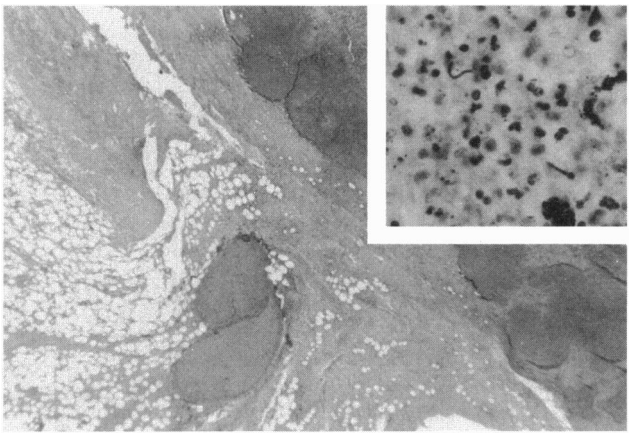

FIG. 3. Photomicrograph of a thoracic lymph node with hemorrhage and necrosis and adjacent hemorrhagic mediastinitis in case 39. (Hematoxylin–eosin stain; ×25.) (*Inset*) Higher magnification photomicrograph of the same section demonstrates lymph node necrosis with karyorrhectic debris, macrophages containing anthracotic pigment, and *B. anthracis* organisms. (Brown–Brenn stain; ×375.)

tered in the submucosa where the blood supply is most prominent. These lesions are analogous to the submucosal metastases of hematogenously disseminated highly malignant neoplasms. The mucosa was present over even the largest hemorrhagic lesions that in some cases extended through the muscularis propria, further suggesting that the infection arrived in the submucosa via the bloodstream rather than entering the mucosa from the gastrointestinal lumen. In fact, Gram-positive bacilli were observed microscopically in blood vessels of the intestinal submucosa. In 4 of the 11 reported cases of the pathology of fatal inhalational anthrax published in the English language since 1960, intestinal lesions presumably of hematogenous origin were described (6, 7, 9, 10–13). Moreover, the classic Russian pathology text by Davidovsky (18) emphasizes that in 90% of cases with gastrointestinal lesions, the enteric pathology occurs because of hematogenous spread of bacilli from a cutaneous or respiratory portal of entry. Although a study of the pathology of epidemiologically diagnosed intestinal anthrax is lacking, the best data available suggest that the primary lesion of intestinal anthrax is usually solitary and located in the terminal ileum or cecum (19). The lesions in the present series of cases usually were numerous and involved many regions of the gastrointestinal tract, including in most cases the stomach and jejunum, indicating that the gastrointestinal

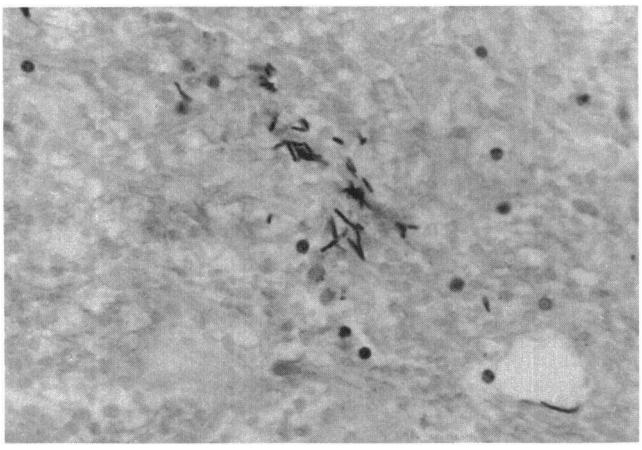

FIG. 4. Photomicrograph of a cluster of Gram-positive *B. anthracis* in a hemorrhagic area of the mediastinum of case 39. (Brown–Brenn stain; ×375.)

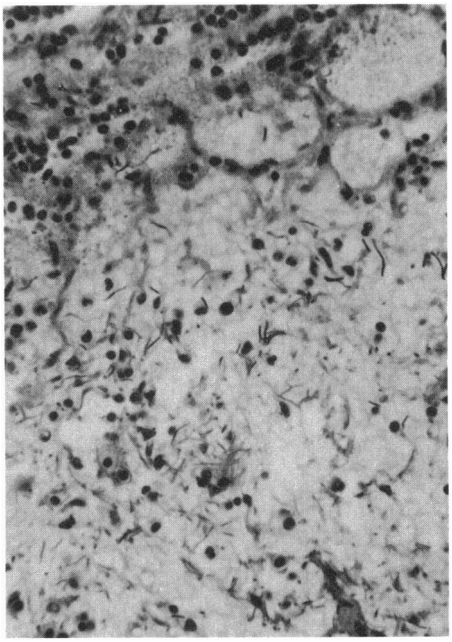

FIG. 5. Photomicrograph of the marginal sinus of a thoracic lymph node in case 39 that is distended by lymph and contains many *B. anthracis* organisms, some of which appear Gram-positive (dark) while others appear Gram-negative (lighter bacilli and filaments). (Brown–Hopps stain; ×250.)

involvement was most likely hematogenous. In 9 of our cases, the route of spread from the pulmonary portal of entry included lymphogenous spread to the mediastinal lymph nodes, followed by hematogenous spread to the intestinal wall and subsequent lymphatic spread to the mesenteric lymph nodes, which were less severely involved than the thoracic lymph nodes. Unfortunately, there is a paucity of information regarding the pathology and pathogenesis of primary intestinal anthrax for comparison with our cases (18–26).

The tragedy of these deaths is compounded by the conditions of secrecy that have impeded elucidation of many facts that potentially would be useful in the future diagnosis and treatment of inhalational anthrax. The paucity of clinical information impairs extensive clinicopathologic correlations including the effects of various therapeutic approaches. Some deaths occurred outside the hospital, at home, or even in the street or in a field. Medical personnel accompanying the emergency transport vehicles often made an initial diag-

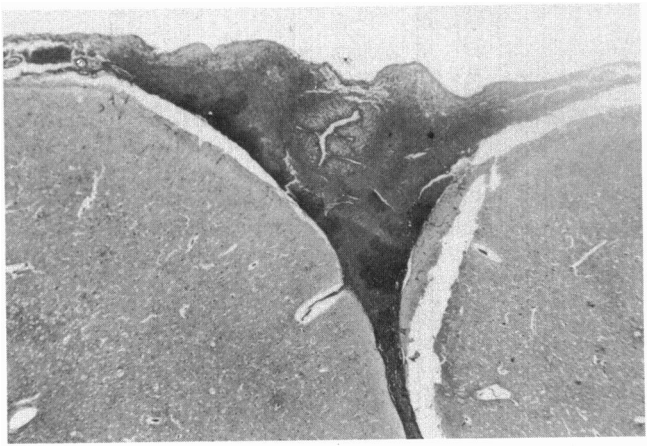

FIG. 6. Photomicrograph of the brain from case 41 shows markedly hemorrhagic leptomeninges. (Hematoxylin–eosin stain; ×15.)

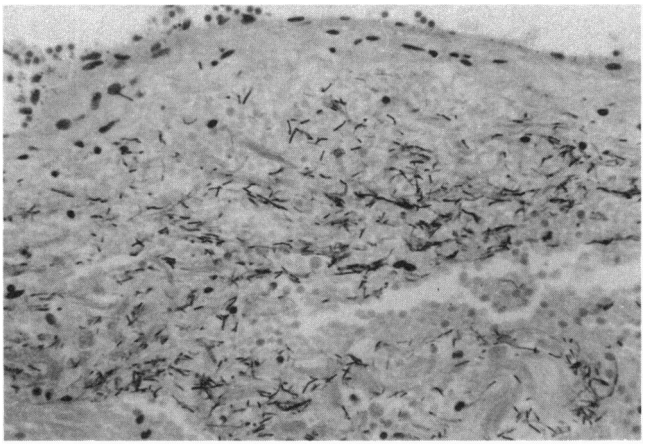

FIG. 7. Photomicrograph of the leptomeninges of case 41 reveals many *B. anthracis* organisms and marked hemorrhage. (Brown–Hopps stain; ×210.)

nosis of pneumonia. The chest pain, which was severe enough to suggest an initial diagnosis of myocardial infarction, undoubtedly resulted from the hemorrhagic thoracic lymphadenitis and mediastinitis.

Previous reports of the cases in this outbreak have excluded description of the thoracic pathology (1). The availability of these new data leads to the conclusion that these patients died because of inhalation of aerosols containing *B. anthracis*. Description of cases of cutaneous anthrax suggests that some, if not all, might have been acquired from animals infected by the same source of spore-containing aerosol. None of these cases of cutaneous anthrax, which is usually not fatal, were represented in this large autopsy series.

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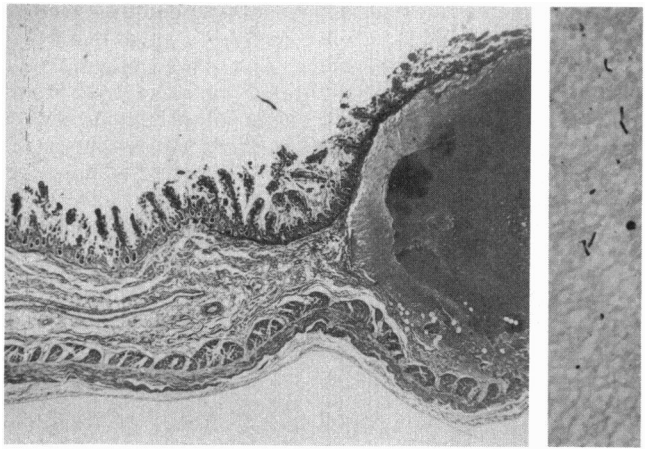

FIG. 8. (*Left*) Photomicrograph of a substantial focus of submucosal hemorrhage in the small intestine that extends into the muscularis propria in case 6. The overlying mucosa is still visible. (Hematoxylin–eosin stain; ×13.) (*Right*) The area of submucosal intestinal hemorrhage contains *B. anthracis* organisms. (Brown–Hopps stain; ×250.)

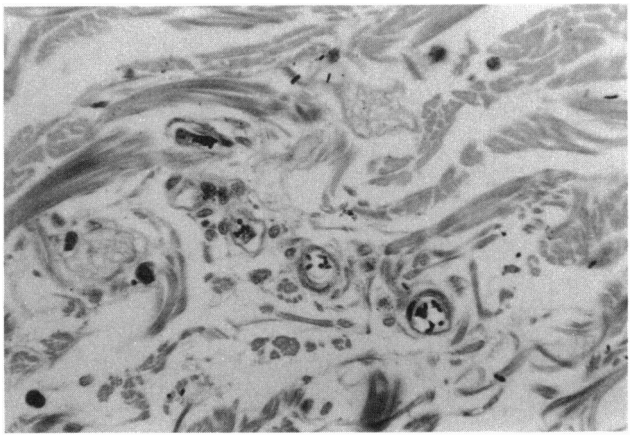

FIG. 9. Photomicrograph of the submucosa of the small intestine of case 6 shows small blood vessels that contain *B. anthracis* organisms. (Brown–Hopps stain; ×300.)

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